To the Editor—The invited article by Wilkin and Gulick [1] excellently summarizes the existing data and recommendations that may be used to decide on when to initiate antiretroviral therapy (ART), except for one area. In their abstract, Wilkin and Gulick [1] state that “large clinical cohorts clearly have demonstrated the benefits of earlier initiation of ART for reducing both HIV-related and non-HIV–related clinical events.” Our interpretation of the existing literature is that large observational studies have supported the findings from randomized, controlled trials that suggest that ART protects patients against AIDS-related opportunistic infections and malignancies, and that this benefit outweighs any risk associated with the initiation of ART for patients with CD4 cell counts $<500$ to $350$ cells/µL. For these types of patients (i.e., with CD4 cell counts $<300$ to $350$ cells/µL), the risk of morbidity and mortality associated with AIDS increases exponentially the lower the CD4 cell count of the patient.

Conversely, there is very little direct evidence from randomized, controlled trials to support the finding that early initiation of ART protects patients against non-HIV–related conditions; the best evidence comes from a study [2] of a small subgroup of 500 patients who were not undergoing ART when they enrolled in the Strategies for Management of Antiretroviral Therapy (SMART) study. Of these 500 patients, 14 developed a non-HIV–related condition during follow-up. Because non-HIV–related conditions predominate over AIDS-related conditions in treatment-naive patients with CD4 cell counts $>350$ cells/µL, our opinion is that the current level of evidence does not support a favorable benefit-to-risk ratio for the initiation of ART for these types of treatment-naive patients (except under certain conditions).

Our interpretation is that, for these treatment-naive patients, the benefit-to-risk ratio remains uncertain. However, this uncertainty can be addressed and, as mentioned by Wilkin and Gulick [1], is under study in the randomized Strategic Timing of Antiretroviral Treatment (START) trial, which is evaluating the risks and benefits of early treatment with a range of important outcomes, including serious non-HIV–related conditions, AIDS, and health care utilization for an appropriate cost-effectiveness analysis (i.e., one based on a reliable estimate of effectiveness). Once completed, the START study will inform guidelines of whether—and possibly in which subgroups—ART should be initiated in persons who are still in the early stages of HIV infection. If the START study finds a favorable benefit-to-risk ratio for early use of ART, then, when applied, this strategy of early use of ART will likely further reduce the reservoir of infectious persons. However, because the ethical justification for use of any type of medicine requires a favorable benefit-to-risk ratio for the person taking the medicine, and because reduction in infectiousness is not of benefit to the person but to his or her partners, this added societal benefit can only be exploited if the START study comes with a favorable benefit-to-risk ratio. Therefore, the completion of the START study, as planned, is urgently needed.

### Acknowledgments

**Potential conflicts of interest.** All authors: no conflicts.

Jens D. Lundgren,1 Andrew N. Phillips,2 and James Neaton2

1Rigshospitalet and the University of Copenhagen, Copenhagen, Denmark; 2Royal Free Campus, University College London Medical School, London, United Kingdom; and 3Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis

### References


Reprints or correspondence: Dr. Jens D. Lundgren, Rigshospitalet and the University of Copenhagen, Copenhagen HIV Programme, Bldg. 211, Panum Institute, Blegdamsvej 38, Copenhagen N, DK-2200 Denmark (jdl@cphiv.dk).

Clinical Infectious Diseases 2009; 48:1162
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DOI: 10.1086/597495

### Reply to Lundgren et al.

To the Editor—We agree with Lundgren et al. [1] that a randomized, controlled trial could provide strong evidence for a favorable benefit-to-risk ratio for earlier initiation of antiretroviral therapy. However, it is interesting to note that antiretroviral treatment guidelines from around the world recently changed to include the recommendation of an earlier initiation of antiretroviral therapy for patients with a CD4 cell count threshold near 350 cells/µL; this change was made primarily on the basis of cohort data, not clinical trials data. For patients with higher CD4 cell counts, non-AIDS–defining events, such as car-

1162 · CID 2009:48 (15 April) · CORRESPONDENCE